

## A Case of HIV Infection with Thrombocytopenia: Association of HIV, Thrombotic Thrombocytopenic Purpura and Brucellosis

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**Abstract** To report a case of HIV infection presenting with thrombotic thrombocytopenic purpura (TTP) and brucellosis that responded well to plasmapheresis and anti-infective therapy. A 64-year-old woman with moderate confusion, fever and pancytopenia was admitted. HIV infection history was taken from her family and she was not receiving antiretroviral therapy last one year. She had generalized purpuric skin lesions. Wright tube agglutination test was found positive with a 1:160 dilution and the patient was diagnosed as brucellosis. Detailed literature search showed brucellosis as a possible cause of TTP. Patient was treated by plasma exchange/fresh frozen plasma and antimicrobials and the response was excellent. Although brucellosis seems to explain the clinical picture of this patient, it is revealed that broad differential diagnosis is needed to reach uncommon diagnosis like TTP particularly in HIV infected patients.

**Keywords** HIV · Brucellosis · Thrombotic thrombocytopenic purpura · Plasma exchange

### Introduction

Thrombotic thrombocytopenic purpura (TTP) is a multi-system disease caused by platelet micro thrombi in various organs. It is a pentad disease including thrombocytopenia, hemolytic anemia, kidney failure, fever, and neurologic symptoms (agitation, disorientation, headache, early or late focal deficits, seizure and coma). Mortality is less than 10% if recognized and treated early/properly. In adults, TTP is idiopathic in about one-third of cases. However, in the rest, TTP is encountered in a variety of clinical situations such as viral, bacterial and mycobacterial infections, drug reactions, connective tissue diseases, solid tumors, bone marrow transplantation and pregnancy. The most famous drugs causing TTP are quinine, ticlopidine and cyclosporine.

Brucellosis is an endemic disease in our country. Although rare, it also has been reported as a causative agent of microangiopathic hemolytic anemia and thrombocytopenia [1–3].

A case of TTP concomitant with brucellosis in a patient with HIV infection is reported here.

### Case Report

A 64-year-old woman was admitted to the hospital, with progressive confusion, disorientation, and high fever for last two days. Seven years before admission, her husband died because of colon cancer and his HIV infection was known. She was diagnosed as HIV infection since then and had been treated by antiretroviral therapy, but history of her CD4 count and the clinical course of infection is not known. Last year she stopped her HIV medications. Also, she lives in an endemic area for brucellosis.

On examination, the patient appeared chronically ill and verbal communication couldn't be made. She was disorientated

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and had moderate confusion. Purpuric skin lesions were present on extremities and abdominal region. The vital signs were normal, except low grade fever ( $38^{\circ}\text{C}$ ). There was no lymphadenopathy. Respiratory and cardiovascular system examinations were unremarkable.

Laboratory tests showed: count of white blood cell 2300  $\mu\text{l}$  (4000–10000  $\mu\text{l}$ ) with 38% neutrophils, 50% lymphocytes, 11% monocytes and 1% basophiles; hemoglobin 8.3 g/dl (11–18 g/dl); platelets 14  $\mu\text{l}$  (150–500  $\mu\text{l}$ ); erythrocyte sedimentation rate 27 mm/h (12–16 mm/h); prothrombin time (PT) 14.6 s (11–15 s); international normalized ratio (INR) 1.27 (0.85–1.28) and activated partial thromboplastin time (APTT) 24.4 s (25.3–34.6 s). The fibrinogen level was 168 mg/dl (150–450 mg/dl), but the D-dimer level was 3.53 ng/ml. The peripheral blood smear showed fragmented erythrocytes and thrombocytopenia (Fig. 1). Direct coombs test was found negative. The bone marrow aspirate was not performed because the test was rejected by the family. Liver function test results were as follows: alanine aminotransferase 19 U/l (< 40 U/l); aspartate aminotransferase 44 U/l (< 41 U/l); lactate dehydrogenase (LDH) 2292 U/l (240–480 U/l) and total bilirubin 3 mg/dl (< 1 mg/dl), 1.68 mg/dl indirect bilirubin (0–0.2 mg/dl). There was mild prerenal azotemia (blood urea nitrogen 36 mg/dl) (5–20 mg/dl) and creatinine was 0.9 mg/dl (0.8–1.2 mg/dl). The urine sediment contained 21 white blood cells and 11 red blood cells per high-power field. The HBsAg, anti-HBc IgM, anti-HAV IgM, and anti-HCV tests were negative. CD4 T lymphocyte count was 99 and HIV RNA was 1,160,000 copy/ml. Abdominal ultrasonography revealed hepatosteatosis. The chest radiograph was normal. The highly active antiretroviral therapy (HAART) (tenofovir + emtricitabin + efavirenz) was started. While investigating the etiology of fever and pancytopenia, a positive agglutination test (Wright agglutination test) for brucellosis was documented at a titer of 1/160 on

the third day after admission. The detection of high antibody titers ( $\geq 1/160$ ) was considered diagnostic (specificity 100%) association with a compatible clinical presentation [4]. Combination of doxycycline (100 mg twice a day, for 6 weeks) and rifampicin (300 mg twice a day) for brucellosis was started. At the beginning, neurobrucellosis was suspected due to the presence of neurologic symptoms. However, examination of cerebrospinal fluid (CSF) sample could not be done because of profound thrombocytopenia. Cerebral computed tomography with contrast agent was found to be normal except minimal cerebral atrophy. Cerebral MRI showed bilateral fronto-parietal multiple ischemic lesions (Fig. 2).

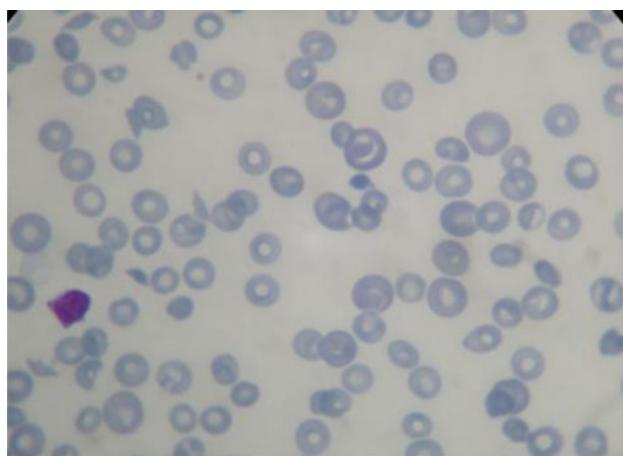
With these clinical and laboratory findings, the patient was diagnosed as TTP and brucellosis in a case with HIV infection. Therapeutic plasma exchange plus fresh frozen plasma replacement were commenced. There was a significant improvement during treatment and she gained consciousness by day 11. During the follow up, after plasmapheresis platelet counts were 76,000, 116,000, 161,000/ $\text{mm}^3$  and LDH levels were 837, 587 and 319 U/l, on days 7, 15 and 25, respectively.

The patient was discharged on the 20th day, with maintenance therapy of doxycycline and rifampicin. There was no neurological sequel on follow-up after treatment completion (12 weeks). The patient had normal clinical and laboratory values on her HAART therapy.

## Discussion

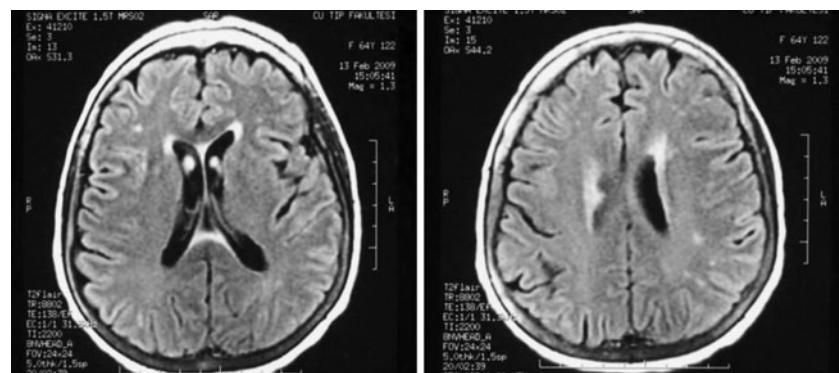
Brucellosis is an important zoonotic disease, and it remains a worldwide public health problem. This disease is epidemic in our country. Humans acquire the infection through the consumption of raw milk products, cheese and raw meat or direct animal exposure [5]. In Turkey, about 18,000 new cases of brucellosis are diagnosed each year [6]. The diagnosis of acute brucellosis in this case was based on the presence of clinical signs and symptoms with 1:160 tube agglutination test [7]. The incidence of pancytopenia in patients with brucellosis is between 3 and 21%. However microangiopathic hemolytic anemias associated with brucellosis have rarely been reported [8–11].

Our patient had hemolytic anemia, thrombocytopenia, schistocytes in the blood smear, increased serum LDH, fever, and neurological symptoms and these findings were compatible with TTP. The patient's test results did not show disseminated intravascular coagulopathy (DIC) with normal PT and fibrinogen levels. Microangiopathic hemolytic anemia caused by bacterial agents may occur due to release of circulating endotoxins and/or immune complexes in the circulation, which may result in alterations in the function of several organs [12, 13]. *Brucella* can form endothelial



**Fig. 1** The peripheral blood film showed fragmented erythrocytes and thrombocytopenia

**Fig. 2** Bifrontoparietal multiple ischemic lesions on cerebral MRI



damage induced directly, or indirectly through toxins or cytokines, and may cause HUS or TTP like diseases. HUS and TTP are syndromes characterized by microangiopathic hemolytic anemia, and thrombocytopenia in which endothelial dysfunction appears to be an important factor in the sequence of events leading to micro vascular thrombosis [9]. Neurological symptoms usually dominate the clinical picture of TTP. In neurobrucellosis, diagnosis depends on the isolation of the organism from the CSF, but this could be rarely possible. Alternatively, serological diagnosis can be performed by the agglutination of CSF. Our case had neurological signs and neurobrucellosis and TTP related CNS signs were two differential diagnoses. Neurobrucellosis couldn't be rule out completely, but rapid resolving of symptoms with TTP treatment was thought the diagnosis as TTP.

On the other hand, TTP can be observed in the context of HIV infection. The etiology of thrombocytopenia in HIV patients may be due to direct infection of megakaryocytes by the virus, immune-mediated destruction, impaired hematopoiesis, toxic effects from medications and microangiopathic anemia syndromes. While the pathogenesis of ITP is usually considered to be autoimmune, that of TTP remains an enigma [14].

The management of TTP requires the treatment of underlying disorder [13]. Additionally plasma exchange is usually employed with the rationale of restoring a component that is missing in the patient's plasma, possibly an enzyme, that by modulating protease activity of Willebrand factor in handling may prevent abnormal fragmentation of that molecule during the acute phase of the disease [15]. Therefore, specific therapy should be started as soon as the diagnosis of the predisposing condition has been established in order to affect disease recovery and minimize the risk of sequel. The treatment recommendation is to continue therapy until complete disease remission is achieved [13]. In our patient, a rapid improvement in platelet count, LDH level, hemolytic anemia and neurologic symptoms was observed with treatment of fresh-frozen plasma infusions and plasma exchange combined with specific

antimicrobial therapy and HAART. In our case, it is impossible to dissect the cause of TTP; it may be due to *Brucella* infection or HIV infection.

## Conclusion

Brucellosis can induce several hematological abnormalities including TTP/TTP like disease. In our case, TTP could be related of two clinical condition, brucellosis and HIV infection. Brucellosis should be considered in patients with HIV infection whose blood work reveals microangiopathic hemolytic anemia, severe thrombocytopenia or pancytopenia, contributing to the morbidity and mortality of the patients. This case shows that therapy of underlying infection together with specific therapy for TTP may be a successful treatment option.

While mortality rate of TTP patients without treatment is above 90%, it can be decreased fever than 10% with early diagnosis and appropriate treatment. It can be said that etiology is complicated, because of the coincidence of two different situations that can cause TTP in our case. Although brucellosis seems to explain the clinical picture of this patient, it is revealed that broad differential diagnosis is needed to reach uncommon diagnosis like TTP particularly in HIV infected patients. In HIV infected patients, situations accompanied especially by fever and blurred consciousness, TTP should be suspected and specific treatment should be given after diagnosis.

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